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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,709	07/27/2001	Michael D. Doyle	001-1	8247

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EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	4

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/916,709	DOYLE ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☒ Claim(s) *1-3 and 6* is/are objected to.

8)☒ Claim(s) *1-6* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' election Specie A (a method using a microarray) and Specie C (biological data analyses types which are mRNAs) in Paper No. 7, filed 2/24/03, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The corrected drawings, filed 2/24/03, have been approved by the draftsman.

Claims herein under examination are claims 1-6.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it does not claim priority to the provisional application.

Claim Objections

Claims 2, 3, and 6 are objected to because of the following informalities:
Claim 3 fails to end with a period. Claims 2 and 3 recite the term "acts" which should be in the singular form as the limitations in each of these claims only refers to a single act as stated in lines 3 and 4 of both claims. Claim 6 has improper dependency (claim 6 cannot properly be dependent from itself). Appropriate correction is required.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, such as on page 2, line 10, and elsewhere. Applicant is

required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The disclosure is objected to because of the following informality: there is a blank space for the provisional application number on page 1, line 7.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the phrase "(biological) gene expression data" which is vague and indefinite. Due to the presence of parentheses, it is unclear if only biological gene expression data or other biological data is obtained. Removal of the parentheses is requested.

Claims 5 and 6 are vague and indefinite due to the unclarity of citing an abbreviation, such as 3-D, on lines 5, 6, and 11 (claim 5) and line 3 (claim 6). Correction is suggested by amending in of the full name in parentheses.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heppelmann et al. (Journal of Microscopy, Vol. 156, Pt. 2, 1989, pages 163-172) in view of Cole et al. (Nature Genetics supplement, Vol. 21, 1999, pages 38-41), Farr et al. (P/N 5,811,231), and Emmert-Buck et al. (Science, Vol. 274, 1996, pages 998-1001).

Heppelmann et al. describe methods for creating multidimensional morphological reconstruction of biological data characterizing a biological tissue sample by cutting histologically thin sections of tissue in two sets of alternating serial sample sections (page 163, lines 1-12) as stated in claims 1 (lines 1-5), 4 (lines 1-5), and 5 (lines 1-4). Heppelmann et al. describe performing these three dimensional reconstructions with graphical techniques and computer-aided methods (page 163, lines 13-14) featuring a spatial matrix of image data as seen in Figure 4 as stated in claims 1 (lines 6-7), 4 (lines 8-9), and 5 (lines 6-7). Heppelmann et al. describe cutting the second set of sections (for ultrastructural examination) and mounting them

on single-slot grids to be further examined (page 164, last paragraph) as stated in claim 1 (lines 8-13). Heppelmann et al. describe the sections were mounted in sequence on grids (page 165, lines 12-14) which is reasonably interpreted to be indexed as it has grids with each individual samples placed in a known location as stated in claims 1, 4 (lines 12-20), and 5 (line 5).

Heppelmann et al. describe histologically-staining the first set of sections and adding a coverslip (page 164, fifth paragraph) which could be used for light microscopy reconstructions (page 163, lines 4-5) as stated in claim 4 (lines 6-7). Heppelmann et al. describe that the second set of tissue sections are covered with a synthetic membrane which is then further cut (page 164, paragraphs 6 and 7) as stated in claim 4 (lines 10-11).

Heppelmann et al. do not teach using a microarray and biological data analyses type which involve mRNA as elected in the species elections. Heppelmann et al. do not teach linking these data to each indexed tissue sample in the multidimensional morphological matrix. Heppelmann et al. do not analyze tissue with monoclonal antibodies or obtain gene expression data and superimpose them on the multidimensional morphological matrix of image data to display correlating values of data with corresponding locations on the matrix.

Cole et al. describe a model for integrating three dimensional expression data obtained using a microarray involving mRNA analysis (page 38, abstract (lines 5-6) and col. 1 (lines 1-4)). Cole et al. discuss cutting tissue in transverse cross-sections (representing X and Y dimensions) available for microdissection and recutting adjacent serial sections in the Z dimension (page 40, col. 1, lines 7-14) which is used to create a multidimensional morphological spatial matrix of image data as seen in Figure 1. Cole et al. discuss the placement of tissue on slides (page 40, col. 1, lines 11-12) and other newly developed fixation and embedding strategies

(page 39, col. 2, lines 15-16). Cole et al. describe methods of preparing microarrays from microdissected cells (page 40, col. 1, lines 19-25 and 37-39). Cole et al. discuss that the above processes allows for the determination of exact physical relationships between morphological data (one set) on which to overlay gene expression data (second set)(page 40, col. 1, lines 14-17 and col. 2, lines 16-24) as stated in claims 1 and 5. Cole et al. describe viewing this information on computers and displaying a data chart in three dimensions (page 40, col. 2, lines 26-38) as stated in claims 1 and 5. Cole et al. show images of stained tissue sample sections obtained from light microscopy (Figure 1, molecular view) as stated in claim 4.

Farr et al. describe a method of measuring biological data, particularly as gene expression levels from specific organs of animal tissues to characterize and identify cellular and subcellular effects of potential toxins on an animal cell (col. 2, lines 52-62 and col. 6, lines 15-23). Farr et al. describe starting experiments with tissue sample and cell lines (col. 6, lines 15-23). Farr et al. describe the results graphically in Figures 1-11 (col. 31, lines 5-6) which consist of multidimensional (3D) representations of the biological data. As can be seen in the Figures 1-11, each data column is indexed and to a particular set of conditions, such as the expression of an enzyme under control of different promoters in the presence of varying concentrations of a test compound (col. 3, lines 24-67). Each of these particular set of conditions was tested with genetic material bound to a solid support membrane which was placed on a 96-well plate (col. 20, lines 53-67; col. 26, lines 9-11; and col. 29, lines 49-51) which allowed for proper indexing and correlation of each set of test conditions to the resulting graphical representations described above as stated in claims 1, 4, 5, and 6. Farr et al. describe an autoradiograph taped to a 96-well plate holder to align the radioactive dots with the holes of the plate holder so that each well is

quantified according it each well position (col. 28, lines 23-27) which is a form of image data. Farr et al. describe correlating the results and creating profiles (col. 28, lines 30-32) as stated in claim 6. Farr et al. describe analyzing assays using antibodies to detect proteins (col. 19, lines 55-67 and col. 20, lines 1-14) with expression levels being regulated by interactions between surface receptors and ligands (col. 4, lines 52-55) as stated in claim 2. Farr et al. describe the method to include detecting levels of mRNA (col. 20, lines 25-67) as stated in claim 3.

Emmert-Buck et al. describe a film or membrane applied to the surface of a tissue section on a glass slide (abstract, lines 3-5). Emmert-Buck et al. describe a laser applied to specific locations the film to procure specifically targeted cells that can then be transferred (abstract, lines 5-9) which suggests incising grid patterns of the tissue and selecting only particular subsections.

Cole et al. state that gene expression microarrays hold great promise in studies of human disease states (abstract, line 1). While some technical issues have yet to be addressed, other precise measurement techniques are at hand to view molecular anatomy of normal cells and their disease counterparts (Cole et al., abstract). Farr et al. state the need for quick, inexpensive and reliable alternatives to toxicity testing in animals (col. 2, lines 11-13) such as using techniques of measuring transcription and translation levels of genes (col. 2, lines 52-62). Farr et al. state the kits and methods of their invention yield rapid and direct information about the nature of a compound's action on mammalian cells (col. 3, lines 12-21). Farr et al. also state that the basic construction of the kits, processes, and products of their invention can be altered to provide other embodiments (col. 32, lines 14-21). Heppelmann et al. state that complex morphological structures cannot be fully appreciated without three-dimensional reconstruction (page 163, lines 15-16). Heppelmann et al. point out that stacking of contoured sections for reconstruction is an

old technique that is now aided by graphical methods and computers (page 163, lines 16-21). A skilled artisan in the art would have been motivated to improve the methods of representing biological data via direct comparisons of genetic expression and morphological data as stated by Cole et al. (page 40, col. 2, lines 21-28) in order to precisely identify and characterize biological effects on certain tissues as stated by Farr et al. (abstract, lines 1-12). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to utilize improved methods of comparison of multidimensional graphic data expression representation to microscopy data, as stated by Cole et al. (page 40, col. 2, lines 21-28) via three-dimensional histological techniques to increase understanding of complex morphological structures as stated by Heppelmann et al. (page 163, lines 15-16 and page 171, lines 11-13), using simple and precision tissue extraction with laser capture microdissection that minimizes contamination, as stated by Emmert-Buck (abstract and page 998, col. 3, lines 2-6 and 12-15), and displaying the gene expression data in easy-to-read three-dimensional graphs as shown by Farr et al. (such as Figure 1), because these exact and efficient techniques would improve accuracy and visual representation for easy interpretation of correlations between the two types of data available to scientists at the time of the invention.

Thus, Heppelmann et al., in view of Cole et al., Farr et al., and Emmert-Buck et al., motivate the instant invention.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax

Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (703) 308-6043. The examiner can normally be reached Monday through Friday from 8 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

April 7, 2003

ARDIN H. MARSCHEL
PRIMARY EXAMINER